REMARKS/ARGUMENTS

The present application was the subject of an Office Action mailed on April 22, 2008. Claims 46-53, 56-64, 72-80, 82-89 and 189-211 were rejected as unpatentable over Hoffman (US 2002/0165146), taken alone or in combination with Skrabanja (US 5,929,028). In this response, claims 50, 194 and 202 have been cancelled, and new claims 212-215 have been added. The pending claims therefore are 46-49, 51-53, 56-64, 72-80, 82-89, 189-193, 195-201, and 203-215.

Hoffman has been cited as teaching formulations of FSH including cresol or phenol. The Hoffman application has also been cited as indicating that other additives such as Tween 20, Pluronic F68, poloxamer 184, or poloxamer 188 can be added to reduce aggregation. Skrabanja has been cited as suggesting the combination of FSH and LH.

The Hoffman application does recite the use of solubilizers such as Tween 20, etc. in FSH formulations. However, numerous other excipients are also identified, including preservatives, isotonicity agents, buffers, antioxidants, and preservative enhancers. Further, Hoffman fails to provide an enabling disclosure of such combinations, which range in the millions. Hoffman itself recognizes the difficulties of preparing stable protein formulations, and the examples in Hoffman do not include any formulations which contain excipients other than preservatives and buffers. No formulations including solubilizers are exemplified. A person of ordinary skill in the art would not understand Hoffman as teaching the viability of each of the vast numbers of combinations which could be theorized from the disclosure.

Regarding the named "solubilizers", the Hoffman application generally describes the "optional" use of:

> "pharmaceutically acceptable solubilizers like Tween 20 (polyoxyethylene (20) sorbitan monolaurate), Tween 40 (polyoxyethylene (20) sorbitan monopalmitate), Tween 80 (polyoxyethylene polyoxypropylene block copolymers), and PEG (polyethylene glycol) or non-ionic surfactants such as

> polysorbate 20 or 80 or poloxamer 184 or 188, Pluronic® polyls, other block co-polymers, and the chelators such as EDTA and EGTA . . . to reduce aggregation." Hoffman, [0100].

This is simply a laundry list of such materials with no suggestion as to which would work in a given formulation. Indeed, the examples in the Hoffman application do not include any formulations which include any of the foregoing solubilizers.

Skrabanja does teach the combination of FSH and LH. However, Skrabanja also notes the pervasive problem in attempting to prepare stable protein formulations:

> "The stability of proteins in aqueous formulations is generally a problem in [sic] pharmaceutical industry. Likewise the stability of aqueous solutions of the gonadotropins is insufficient to allow storage for longer times. This is especially true for preparations containing the very pure gonadotropins, prepared using recombinant DNA methods, in relatively dilute solutions." Skrabanja, column 2, lines 21-27.

Further, Skrabanja only indicates the preparation of a stable formulation when using "stabilizing amounts" of both a polycarboxylic acid or salt, along with a thioether compound.

As was well known in the art at the time of the making of the present invention, formulations including proteins, particularly heterodimeric proteins such as FSH, are susceptible to many avenues of degradation, and the preparation of stable formulations of FSH has been a long-standing problem. Numerous references confirm the difficulty of preparing stable protein formulations, including both of the cited references.

The use of phenolic compounds (including benzyl alcohol and m-cresol) as antibacterial agents is discussed at length in the article "Aggregation of recombinant human growth hormone induced by phenolic compounds," Maa et al., International Journal of Pharmaceutics 140 (1996), 155-168. Maa et al. noted that such preservatives have "adverse effects when added to protein formulations" and that the theories for such effects included Van der Waals forces, hydrophobic interactions, hydrogen bonding, electrostatic repulsion and chemical reactions, concluding that

the "mechanism causing protein destabilization is unclear." Maa et al., at 156. In that study, "each rhGH solution containing a phenolic compound was either opalescent or cloudy, attributed to particulates formation." Maa et al., at 159. This led to the conclusion that "the selection of a phenolic anti-microbial preservative for a liquid protein formulation should be concerned with its effect on protein's short-term and long-term stability." Maa et al., at 168.

As a heterodimer held together by noncovalent interactions, FSH was known to be especially susceptible to the deleterious effects of excipients, and the effects are not straightforward. At low concentrations, there is the potential for FSH to dissociate, while at high concentrations FSH tends to aggregate – either of which renders the FSH ineffective. Further, organic solvents such as m-cresol are particularly destabilizing.

It is clear that the state of the art at the time the invention was made was that the preparation of stable FSH formulations was known to be a difficult proposition, with essentially any change or addition as to excipient(s) having the potential of resulting in instability. Applicants submit that exhaustive lists of widely diverse components, as found in Hoffman and Skrabanja, do not provide predictability as to individual combinations, particularly in view of the state of the art and the level of skill in the art of protein formulating.

Claims 46-53, 56-64 and 198-211 have been rejected as unpatentable over Hoffman. Claims 50 and 202 have been cancelled, and the rejection of those claims is thereby obviated. The other claims have been amended herein, and are currently directed to combinations of FSH, a diluent, poloxamer 188, and m-cresol or phenol. As the application points out, the use of poloxamer 188 (Pluronic F68) with m-cresol or phenol solves a problem of precipitation and provides "clear solutions" which are free of visible particles. See page 26, line 16, and page 45, Table 8. The application specifically indicates that poloxamer 188 provides "a stable

formulation that avoids the problem of precipitation in the presence of a bacteriostatic agent, such as m-cresol and phenol." See page 12, lines 28-35.

Hoffman suggests the use of its identified solubilizers as an optional excipient with the specific purpose being "to reduce aggregation". Instead, applicants discovered that the very first listed solubilizer, Tween 20, is unsuitable when used with m-cresol or phenol as it resulted in a "turbid or milky solution". See page 12, lines 28-35. In contrast to the supposed teaching of Hoffman, the applicants found:

> "From visual examination of the formulations, it was determined that TWEEN 20 cannot be used with m-cresol and phenol because FSH formulations containing TWEEN 20 and m-cresol or TWEEN 20 and phenol presented a white opalescent suspension. In contrast, FSH formulations containing Pluronic F68 did not exhibit this problem with m-cresol and phenol. The use of Pluronic F68 permits the use of phenol and m-cresol." See page 33, lines 1-7.

This result demonstrates the lack of predictability for stability of protein formulations, and confirms the lack of a meaningful teaching by references such as the cited Hoffman application when lengthy lists of theoretical excipients are recited. This is also in distinct contrast to the suggestion in the cited Skrabanja patent, which states that Tween 20 is "especially preferred" for use in its FSH formulations.

Applicants submit that this is an unobvious advantage for the formulations including m-cresol or phenol in combination with poloxamer 188, and that claims 46-53, 56-64 and 198-211 are therefore patentable over the cited art.

By this amendment, new claims 212-215 have been added. These claims are presented with the transitional term "consisting essentially of". Claims 212-213 are directed to formulations including FSH, a diluent, m-cresol and poloxamer 188, as well as sucrose, methionine, and phosphate buffer. Claims 214-215 are directed to formulations including FSH,

LH, a diluent, phenol and poloxamer 188, as well as sucrose, methionine, and a phosphate buffer. These claims are further distinguished from the cited art in this respect.

Claims 72-80, 82-89 and 189-197 have been rejected as unpatentable over Hoffman in view of Skrabanja. Claim 194 has been cancelled, and the rejection of that claim is thereby obviated. The other claims have been amended herein, and are currently directed to combinations of FSH, LH, a diluent, poloxamer 188, and m-cresol or phenol. As noted previously, the application points out that the use of poloxamer 188 solves a problem of precipitation and provides "clear solutions" which are free of visible particles, thereby providing "a stable formulation that avoids the problem of precipitation in the presence of a bacteriostatic agent, such as m-cresol and phenol."

Skrabanja has been cited as teaching the combination of FSH and LH in a pharmaceutical formulation. However, this reference again notes the difficulties in preparing stable protein formulations, and therefore does not teach that FSH and LH can predictably be combined with other excipients, except to the extent of the formulations described therein. Skrabanja expressly indicates that the stability of the Skrabanja formulations is dependent on the combined use of a polycarboxylic acid, as well as a thioether. It is also notable that Skrabanja does not teach any formulations including an anti-microbial agent.

Moreover, applicants submit that it would not be obvious to combine the teachings of Skrabanja and Hoffman to obtain the present invention. Skrabanja describes the difficulty in preparing FSH formulations, and particularly cites to a problem with the gonadatropins being adsorbed by container walls:

> "The formulation of the invention preferably also comprises one or more nonionic surfactants. *These surfactants act as anti-adsorption agents and prevent the loss of the gonadotropin as a result of adsorption of the protein to the walls of the container in which the formulations are kept.* The addition of an anti-

> adsorption agent to the formulations of the invention is *especially required when the formulations comprise a recombinant gonadotropin in low concentrations*." Skrabanja, column 5, lines 15-22 (emphasis added).

In contrast, Hoffman only discloses the use of "solubilizers" in order "to reduce aggregation". A person of ordinary skill in the art would understand these to be different issues – adsorption by the container walls versus aggregation.

Thus, combining the Hoffman and Skrabanja references would not be within the ordinary skill in the art. Hoffman relates only to FSH; Skrabanja includes both FSH and LH, and one could not predict the effect caused by the additional presence of the LH. Hoffman includes anti-microbial agents; Skrabanja does not. Hoffman mentions numerous other excipients that may or may not be present; Skrabanja requires the presence of a polycarboxylic acid, as well as a thioether, in order to obtain stability. Hoffman mentions the use of solubilizers as simply an "optional" matter in order to reduce aggregation; Skrabanja identifies the use of nonionic surfactants in order to prevent adsorption of the FSH (and/or LH) by the container walls. In the setting of severe stability issues for protein formulations, it would not be obvious to combine these disparate references.

As stated in Skrabanja, the adsorption problem is particularly critical for formulations comprising recombinant FSH in low concentrations. These are also further distanced from the teachings of Hoffman which is only concerned with aggregation. Consequently, claims 53, 61, 62, 86, 87, 195, 205, and 212-215, directed to recombinant FSH, are even more distinguishable from the cited references and are patentable on that additional basis.

Reconsideration of the above-identified patent application, as amended and in view of the foregoing remarks, is respectfully requested. An action on the merits and allowance of the

claims is solicited. If the Examiner believes that it would expedite examination of this case, the Examiner is requested to contact the undersigned directly.

Respectfully submitted,

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